REMARKS

The claims have been amended to more clearly describe the current invention and do not introduce new matter. In particular, as the Examiner suggested, claim 27 has been amended to be independent and includes all of the limitations previously contained in the base claim. Therefore, claim 27 should now be allowable. Additionally, claim 16 has been amended to eliminate rejection based on improper product use claims while claim 23 has been amended to include formula I and define the R1 and R2 variables.

Election/ Restriction

The Examiner again argues that restriction is appropriate, disagreeing that the common core is represented by the phosphonooxymethyl group because [R] is so diverse in scope that a prior art reference anticipating the claims under 35 U.S.C. § 102(b) with respect to one member would not render obvious the same claim under 35 U.S.C. 103(a) with respect to another member. Additionally, the Examiner argues that the prodrug precursors represent independent and distinct structures with no reasonable assurance that these different structures can be cleaved by the human or animal body and function. Finally, the Examiner urges that the compounds are classified in different classes based on the value of the [R] variable and therefore constitute a burdensome search. Applicants respectfully traverse. Applicants have enclosed a list of publications that provide objective evidence that prodrug precursors are cleaved and function appropriately.

To summarize, phosphatases are responsible for the prodrug cleavage that occurs and releases the drug. Human phosphatases include two main groups, acidic phosphatases and alkaline phosphatases. The alkaline phosphatases are membrane associated and fairly ubiquitous in the body (see references 1-5). The structural homology and activity appear to be conserved across species. Alkaline phosphatase exists as a dimer of two identical monomers (see reference 1). One active site is on the surface of each monomer and accessibility calculations have shown that the active pocket barely accommodates inorganic phosphate. This suggests that the non-phosphoryl portion of the substrate is exposed on the enzyme surface during hydrolysis and that

steric hindrance around the hydrolysis site may play an important role in conversion rates (see references 6 and 7). For example, a study using *E. coli* alkaline phosphatase catalyzed hydrolysis of a series of simple alkyl phosphates demonstrated that the sterically hindered alcohol of *t*-butyl phosphate had no observable conversion to the parent alcohol while both primary (methyl) and secondary (isopropyl) alkyl phosphates were cleaved (see reference 7). The current invention uses the methylene bridge to spatially remove the phosphate moiety from the sterically hindered site [the sum of which comprises the phosphonooxymethyl moiety; $-O(CH_2)_nOPO(OR_1)(OR_2)$], thereby allowing greater degrees of freedom for docking of the phosphate ester in the active site.

A number of directly phosphorylated monophosphate esters of drugs have been shown to be readily and completely converted *in vivo* to the pharmacologically active parent drug as a result of the action of phosphatases. Examples include dexamethoazone (a primary alcohol; reference 8), arabinofuranosyl adenine (an unhindered secondary alcohol; reference 9), triamcinolone (a primary alcohol; reference 10), clindamycin (an unhindered secondary alcohol; references 11 and 12), betamethasone (a primary alcohol; reference 13), and methylprednisolone (a primary alcohol; references 14 and 15). Based on these and other examples, it is readily accepted by the scientific community that non-sterically hindered phosphate esters of drugs will be readily converted *in vivo* to the parent compounds and, in fact, numerous U.S. patents have been issued for various prodrugs and prodrug families. Hence, the Examiner's concern with respect to cleavability seems unfounded.

The Examiner's contention that the variability in [R] constitutes a burdensome search is no basis for a restriction requirement. As stated in *In re Weber* (580 F.2d 455, 458):

> " It is elementary patent law that the number of 'species' 'covered' by a patent having a generic claim is virtually without limit notwithstanding the limitation of Rule 141 to five species 'specifically claimed.' So the discretionary power to limit one application to one invention is no excuse at all for refusing to examine a broad generic claim – no matter how broad, which means no matter how many independently patentable inventions may fall within it."

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Hence, a species election requirement is more appropriate, not a restriction requirement. The applicants elected Propofol as a species with traverse. Applicants again request that the Examiner reconsider the restriction requirement and prosecute the application in total, using Propofol as a species representing the generic claims. Applicants do not concede that defining R as both alcohol-containing and phenol-containing pharmaceutical compounds requires restriction requirement. Applicants have, however, restricted the claims to define [R] as only phenol-containing pharmaceutical compounds in order to reduce the Examiners search, and will pursue claims directed towards [R] defined as alcohol-containing pharmaceutical compounds in a divisional application.

Objections to Claims

The Examiner has objected to claims 1-5, 8-12 and 16-22 as being directed to an improper Markush Group, urging that there is no common core present which is essential to the utility. Claims 1 and 8 have been amended to cover only phenol-containing pharmaceutical compounds. Hence claims 1, 8 and 16 now have as their common core both the phosphonooxymethyl moiety and a phenol-containing pharmaceutical compound. The Examiner's objection is thereby overcome.

Rejections Under 35 U.S.C. §112

The Examiner has rejected claims 23, 24, 30 and 31 as indefinite since there is no formula I present in claim 23 and variables R1 and R2 are not defined. Claim 23 has been amended to include the formula I, and the definitions of R1 and R2 have been added, thereby overcoming the rejection.

Accordingly, in view of the above amendments and remarks, all the claims remaining in the case as amended are submitted as defining non-obvious, patentable subject matter.

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Reconsideration of the rejections and allowance of the claims of the present application are respectfully requested.

If the Examiner has any questions concerning this application, the Examiner is requested to contact the undersigned at (714) 708-8555 in the Southern California area.

Pursuant to 37 C.F.R. 1.17 and 1.136(a), the applicants respectfully request a two (2) month extension of time for filing this Response in connection with the present application and the required fee of $380.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope to: Commissioner of Patents and Trademarks, Washington D.C. 20231 on: 3-21-2000
(Date of deposit)

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Respectfully submitted,

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LRS/SWG:lm

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